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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,259	KIENER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *11 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-16 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/7/06, 6/10/05, and 6/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 are pending.

2. Applicant's election with traverse of Group II, claims 1-10, 12-16, 18-23, drawn to a method of treating a hypoproliferative cell disorder or disorder involving increased cell death in a patient comprising administering to an EPHA2 antagonistic agent, wherein the antagonistic agent is an antibody filed on 9/28/06, is acknowledged.

Applicant's traversal is on the grounds that a single search would necessarily result in a complete search of the art related to the claims as filed. In addition, Applicants assert that to search and examine the subject matter of the claims as filed would not be a serious burden on the Examiner. This is not found persuasive because the specific EphA2 polypeptide fragment, antibody, a small molecule antagonist, enzymatic activity antagonist, EphrinA1 siRNA or eiRNA molecule and EphrinA1 antisense molecule are recognized divergent subject matter. In addition, the different EphA2 antagonistic agent are distinct because their structures are different and are therefore capable of separate manufacture, use and sale. Therefore the various methods of treating a hypoproliferative cell disorder using a various EphA2 antagonistic agents are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 11 and 17 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-10, 12-16 and 18-23 are under examination as they read on a method of treating a hypoproliferative cell disorder or disorder involving increased cell death in a patient comprising administering to an EPHA2 antagonistic agent, wherein the antagonistic agent is an antibody.

5. Applicant's IDS, filed 2/7/06, 6/10/05 and 6/10/05 (last two has same date), is acknowledged, however, the references A01-A22 were considered (as indicated by Examiner's initials) but crossed out because said references have no publication dates.

6. The specification on page 46, ¶120 is objected to because it contains empty spaces "_____" that needs to be either removed or filled. Correction is required.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The " epithelial and/or endothelial cell " recited in claims 5-6 is indefinite. The claims are comparing the proliferation or survival of a specific cell relative to the untreated cell epithelial and/or endothelial cell. It is unclear how to compare the survival of epithelial cell compared to the endothelial cell for example.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10, 12-16 and 17-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** for a method of treating a hypoprolifertive cell disorder or disorder involving increased cell death in a patient in need comprising administering to said patient a therapeutically effective amount of an "Ehp2 antagonistic agent" in claim 1, wherein said hypoproliferative cell disorder or disorder involving increased cell death is "interstitial cystitis or a lesion associated with IBD" in claim 3, wherein the said EphA2 antagonistic agent is an "antibody or antigen binding fragment thereof" in claim 12, the method further comprising the administration of "one or more additional hypoproliferative cell disorder therapies that do not alter EphA2 expression or activity" in claim 21, wherein said additional hypoproliferative cell disorder therapies that do not alter EphA2 expression or activity consist of an immunomodulatory agent or an anti-urinary tract infection agent in claim 22 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification on page 2, lines 1-2 discloses that the function of EphA2 is not known, but it has been suggested to regulate proliferation, differentiation, and barrier function of colonic epithelium. The specification on page 2, ¶3, discloses that the interaction between EphA2 and Ephrin A1 interaction maintain an epithelial cell barrier that protects the organ and helps regulate over proliferation and growth of epithelial cells. Further the specification on page 4, ¶10,

discloses that an increase in EphA2 levels can increase the proliferation, growth, and/or survival and/or maintain the organization of epithelial and/or endothelial cell layers. The specification asserts that the use of agents that antagonize EphA2, i.e., decrease EphA2-endogenous ligand binding, upregulate EphA2 gene expression and/or translation, increases EphA2 protein stability or protein accumulation, decrease EphA2 cytoplasmic tail phosphorylation, promote EphA2 kinase activity, increase proliferation of EphA2 expression cells, increase survival of EphA2 expression cell, and/or maintain/reconstitute the integrity of an epithelial and/or endothelial cell layer.

However, the phrase an "EphA2 antagonistic agent" in claim 1, is intended to include, but not be limited to proteins, antibodies, nucleic acids, antisense, small molecule and carbohydrate. The specification does not provide a sufficient enabling description of the claimed antagonist. A person of skill in the art is not enabled to make and use any *"antagonist"* including protein, nucleic acids, antisense, small molecule and carbohydrate that treat a hyporoliferative cell disorder or disorder involving increased cell death as encompassed by the full breadth of the claims as currently recited. It was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "antagonists". However, Huang (Pharmacol. Therapeutics 2000 86:201-215) reviews in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and notes that the process required long periods of trial and error testing before suitable compounds could be developed. Similarly, Toole et al (Storming Media: the role of EMMPRIN in Tumor angiogenesis and metastasis, May 2001) teach that antisense cDNA and ribozyme constructs were utilized in an attempt to inhibit EMMPRIN expression TA3/ST cells, however, these constructs were not efficient in blocking EMMPRIN expression and consequently, were inactive in vivo (see the abstract in particular). Further, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictability was summarized by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Wang et al. (JBC 276:49213-49220) show that a single amino acid determines lysophospholipid specificity of the S1P1 (EDG1) and LPA1 (EDG2) phospholipids growth factor receptors (e.g., abstract). Wang et al shows that a single amino acid Glu^{121} in S1P1/EDG1, which corresponds to Gln^{125} in LPA1/EDG2, influences the specificity for S1P or LAP (see page 49213 last ¶). Mutating the Arg-Glu-Gly motif to that is conserved among LPA receptors Arg-Gln-Gly, lead to ligand selectivity switch in concert with the mutations. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the

biological activity and characteristic of a protein. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any antagonist such as a simple or complex organic or inorganic molecule, a peptide, a protein or an oligonucleotide (e.g. anti-sense) are fraught with uncertainties.

While "antagonist" may have a notion of "inhibiting" the function of the claimed EphA2 receptor; there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "antagonist" of EphA2 receptor activity, as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Applicant invention is based on the observation that EphA2 plays a dual role in cellular proliferation regulation, hypoproliferation or hyperproliferation depending on context of the EphA2 phosphorylation and expression in normal (negatively regulate cellular proliferation) versus tumor cell (positively regulate cell proliferation). The specification discloses that the use of agents that antagonize EphA2, i.e., decrease EphA2-endogenous ligand binding, upregulate EphA2 gene expression and/or translation, increases EphA2 protein stability or protein accumulation, decrease EphA2 cytoplasmic tail phosphorylation, promote EphA2 kinase activity, increase proliferation of EphA2 expression cells, increase survival of EphA2 expression cell, and/or maintain/reconstitute the integrity of an epithelial and/or endothelial cell layer.

On the basis of the disclosed correlation of the level of phosphorylation of the EphA2 receptor in epithelial/endothelial cell observation alone (see page 19, lines 20-21), applicant concludes that the scope of the EphA2 antagonist agents encompassed by the claimed invention can have biological activity to induce proliferation and treat interstitial cystitis or a lesion associated with IBD and be provided as pharmaceutical compositions to subjects including human to effectively treat said hypoproliferative cell disorders and induce proliferation. The specification contemplated that anti-EphA2 agonist agents can be used to treat cancer (hyperproliferative disorder) while anti-EphA2 antagonist agents can treat hypoproliferative disorders. No such agents such as anti-Ephrin A1 antibodies were produced or tested, it is unclear if these assay results are predictive of decrease EphA2-endogenous ligand binding, upregulate EphA2 gene expression and/or translation, increases EphA2 protein stability or protein accumulation, decrease EphA2 cytoplasmic tail phosphorylation, promote EphA2 kinase activity, increase proliferation of EphA2 expression cells, increase survival of EphA2 expression cell, and/or maintain/reconstitute the integrity of an epithelial and/or endothelial cell layer.

In order for this therapy to be predictable, the EphA2 expression/phosphorylation must play a role in inducing proliferation of epithelial/ endothelial cells. The only state of the art reference demonstrates an *in vivo* murine model is Pandey *et al* (IDS ref C219) teach that anti-B61 antibodies (i.e., anti-EphrinA1 antibodies) resulted in inhibition of Eck (i.e., EphA2) autophosphorylation in HUVECs (i.e., endothelial cells) treated with TNF-α (see page 568, Figure 3 in particular). Importantly, Pandey *et al* teach that anti-B61 antibodies administered to

the rat corneas has no effect on vascularization in the cornea, while simultaneous administration of TNF-α and anti-B61 resulted in a greatly attenuated angiogenic response (see page 568, 3rd col., 1st in particular). Similarly, Rosenberg *et al* (IDS ref. No. C241) teaches that B61 (EphrinA1 ligand) modulate intestinal epithelial migration and barrier function. Rosenberg et al conclude that functionally, *stimulation of Eck by B61* resulted in *increased* proliferation, *enhanced* barrier function, and *enhanced* restitution of injured epithelial monolayers (see abstract). These findings indicate that anti-Ephrin A1antibody "EphA2 inhibiting agent" has no effect on vascularization in vivo and that EphA2/ligand interaction would induce proliferation. Applicant has no working examples demonstrating an *in vivo* treatment regiment with anti-Ephrin A1 antagonistic antibodies to induce vascularization, and the state of the art taught the "EphA2 antagonist agent", anti-B61 antibody, to have no effect vasculaization. Further, the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method for treating a hypoproliferative cell disorder or disorder involving increased cell death using anti-Ephrin A1 antibodies with a reasonable expectation of success. One skill in the art would concluded that a strategy of using anti-Ephrin A1 antibody in inducing proliferation would require further understanding of the role of EphA2 in proliferation. Applicant's strategy to treat a hypoproliferative cell disorder or disorder involving increased cell death in a patient using anti-EphrinA1 antibodies is fraught with inaccuracies and that these methods are still notably deficient in defining and describing the complexity of EphA2 function in cell proliferative activity. The clinical value of such strategies has been shown by Pandey *et al* and Rosenberg *et al* to be ineffective for inducing proliferation of epithelial/endothelial cell.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-10, 12-16 and 17-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of any a method of treating a hypoprolifertive cell disorder or disorder involving increased cell death in a patient in need comprising administering to said patient a therapeutically effective amount of an "EphA2 antagonistic agent" in claim 1, wherein said hypoproliferative cell disorder or disorder involving increased cell death is "interstitial cystitis or a lesion associated with IBD" in claim 3, wherein the said EphA2 antagonistic agent is an "antibody or antigen binding fragment thereof" in claim 12, the method further comprising the administration of "one or more additional hypoproliferative cell disorder therapies that do not alter EphA2 expression or activity" in claim 21, wherein said additional hypoproliferative cell disorder therapies that do not alter EphA2 expression or activity consist of an immunomodulatory agent or an anti-urinary tract infection agent in claim 22.

Applicant has disclosed only anti-Ephrin A1 antibody; therefore, the skilled artisan cannot envision all the contemplated EphA2 antagonistic agent possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-2, 4-10, 18-20 are rejected under 35 U.S.C. 102(a) as being anticipated by US. Pat. No. 5,824,303 (IDS A44).

The `303 patent teaches and claims a method for treatment of a wound (epithelial-endothelial interactions) in a mammal (hypoproliferative disorders) comprising contacting administering an eck (EphA2) receptor binding protein comprising the amino acid sequence of SEQ ID NO: 1

(EBP) or a fragment thereof (see patented claims 1-3 and 8 in particular). The `303 patent further teaches that the ligand acts as a growth factor to stimulate the proliferation of target cells or the ligand binding may not activate the eck receptor and acts as antagonist for other molecules which activate the receptor and induce in signal transduction (see col., 8, lines 8-12 in particular). The `303 patent teaches that eck (EphA2) receptor is expressed primarily in tissues containing significant amounts of epithelial cells and in the cell lines derived from epithelial cells. A ligand of the eck receptor can stimulate the growth of cells expressing the receptor eck receptor ligands may also be used for the treatment of wounds to promote healing (involve both endothelial and epithelial cells) (see col. 8, lines 14-19. The `303 patent further teaches that fragments or analogs of EBP which bind to but do not activate the eck receptor are useful as EBP antagonists. Administration of an EBP antagonist having affinity for the eck receptor will block receptor binding and activation by circulating EBP (see col., 8, lines 26-34 in particular). Also, the `303 patent teaches that EBP gene is expressed in endothelial cells (see col., 8., lines 45-46 in particular). Finally, the `303 patent teaches a method for the treatment of a wound in a mammal (destruction of epithelial cells) comprising administering an eck receptor ligand (see col., 8, lines 53-55 and Example 9A in particular).

Claims 4-10, 18-20 are included because the cited mechanism of action are inherent properties of the referenced EBP ligand in the absence of evidence to the contrary.

The reference teachings anticipate the claimed invention.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 24, 2006

Maher Haddad

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